Effect of paternal loss-of-function mutations of GNAS on growth during the childhood: a role for XL

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OBJECTIVES

GNAS is a complex imprinted locus which leads to different transcripts characterized by one specific exon 1 and shared exons 2-13, with monoallelic (XL, NESP55) or biallelic (Gₐα) expression. Recent studies suggested that human birth weights were lower with paternal GNAS mutations affecting exons 2–13 (including XL and Gₐα) than with exon 1/intron 1 (specific to Gₐα) mutations, suggesting a role for XL in fetal growth (1). Our aim was to assess the growth, from early childhood to late adolescence, according to the location of the loss-of-function GNAS mutation (exon/intron 1 versus exons 2-13).

METHODS

This retrospective study was conducted on patients with paternal mutations on either exon 1 (group 1: n= 9) or exons 2-13 (group 2: n= 19). Weight (W) and height (H) were compared to sex-specific WHO reference charts, which curves have been created using GraphPad®. Data were gathered into three age groups, with birth data being excluded. Median values of Z-score between the two groups were statistically compared using Mann-Whitney test.

RESULTS

Weight: The difference between groups 1 and 2 disappeared after birth. Despite being born with a severe intrauterine growth retardation, patients displayed a catch-up growth with weight-for-age values within the normal range (from -2 to +2 SD) after 10 years.

Height: Patients from both groups are smaller compared to the WHO normal references. Interestingly patients from group 2 remained significantly smaller than patients from group 1.

CONCLUSIONS

Our results confirm a role for XL in the regulation of fetal growth. After birth, the patients recovered a normal weight during the first few years, despite they were globally smaller than the median references in both groups. Our data implicate a role for the paternal imprinting in the height in these patients.

(1) Richard et al. JCEM 2013 Sep;98(9):E1549–56. The authors did not have any conflict of interest and have not been funded.